ALBERTA HERITAGE FOUNDATION
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TechNote

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ADULT TO ADULT LIVING DONOR LIVER TRANSPLANTATION

Request: This response addressed a request from Alberta Health and Wellness. The objective of this Technote is to evaluate the evidence on the safety and efficacy of adult to adult living donor liver transplantation. The report is intended to provide a distillation of the evidence on the current status of living donor liver transplantation in the treatment of end stage liver disease.

BACKGROUND

The liver is the largest internal organ of the body, weighing between 1.5 and 1.8 kilograms in an adult. It is a complex chemical factory that is essential to life. The liver processes fats, carbohydrates, and amino acids; makes essential proteins such as enzymes and blood clotting factors; stores fat soluble vitamins; produces bile; helps regulate blood cholesterol and glucose; assists in the control of various hormone systems; plays an essential role in immunological defence; and breaks down potentially toxic substances such as alcohol [1-3].

The liver consists of two main (right and left) and two accessory (quadrate and caudate) lobes. Blood enters the liver from the portal vein and hepatic artery and leaves via the hepatic veins [2]. However, the liver is actually composed of eight autonomous segments that have their own separate blood supply and biliary channels; segments II to IV make up the left lobe, V to VIII make up the right lobe, and segment I forms the caudate lobe [2].

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Indications for liver transplantation

End-stage liver disease (ESLD) occurs when functional liver cell mass falls below a critical level. Hepatic failure is either acute or chronic depending on the length of time it takes for the liver to fail. Acute exacerbation of an underlying chronic condition is referred to as acute-on-chronic hepatic failure. ESLD generally results from either obstruction of bile flow, known as cholestatic disease, or disruption of liver cell function. Hepatocellular diseases, such as viral hepatitis or alcoholic cirrhosis, cause liver tissue to become inflamed and necrotic, and typically result in a much faster clinical deterioration than cholestatic disease [4]. The failure of the ailing liver to perform its manifold functions leads to the build up of toxic substances in the body, and is associated with symptoms such as jaundice, muscle wasting, weight loss, bruising, collection of excess fluid in the peritoneal cavity, portal vein hypertension, hepatomegaly, reduced renal function, coagulopathy, and edema. Hepatic encephalopathy is another serious symptom that often occurs in patients with acute hepatic failure. It is characterised by disturbed brain function, which can manifest as personality changes, sleep disturbance, lethargy, lack of muscular coordination, and drowsiness. Severe hepatic encephalopathy results in coma and brain edema, which may cause brain stem herniation [4, 5].

Liver cirrhosis is the twelfth leading cause of adult mortality in the United States and is usually the result of chronic hepatitis C or alcoholic liver disease. Liver transplants have been performed for close to 60 distinct liver diseases [6], but cirrhosis is the most common reason for liver transplantation in North America [4, 7]. Some of the other indications for liver transplantation include cirrhosis resulting from chronic cholestatic disorders (primary and secondary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia); chronic hepatitis (hepatitis B, autoimmune chronic active hepatitis); metabolic disorders (urea cycle anomalies, primary oxalosis, familial amyloid polyneuropathy, hemochromatosis, non-alcoholic steatohepatitis); liver tumours such as hepatocellular carcinoma; trauma; and fulminant liver failure (caused by toxins or drugs such as paracetamol and halothane) [1, 6-8].

Unlike patients with end stage renal disease who can survive with regular renal or peritoneal dialysis, there is currently no effective long-term mechanical or pharmaceutical replacement for a functioning liver. Consequently, the only curative treatment for ESLD is liver transplantation [9, 10].

Liver Transplant Options

Cadaveric donor liver transplantation

The first human liver transplant was performed in the United States in 1963. While initial results were poor, subsequent advances in postoperative immunosuppression regimens, surgical technique, patient selection, and tissue preservation methods

reversed this trend to the extent that liver transplantation is now considered to be the definitive therapy for ESLD [11].

The liver is the second most commonly transplanted human organ after the kidney [12, 13]. The main source of cadaveric livers in Western countries is brain dead donors with beating hearts [11, 14]. Once the cadaveric liver is removed, it is flushed with preserving solution and transported to the recipient's hospital. It then undergoes 'back table' preparation in which superfluous tissue is removed and vascular conduits are reconstructed. The recipient's diseased liver is then replaced with the donor liver, and the vascular and biliary connections are reconstructed [4, 6]. Graft rejection is controlled with an immunosuppression regimen that must be continued for the rest of the patient's life [15]. The one and five year survival rates for adult recipients of cadaveric livers range from 85% to 91% and from 63% to 80%, respectively, for most types of chronic liver disease [7, 12]. Potential postoperative complications include graft rejection, liver dysfunction or failure, biliary problems, hepatic artery thrombosis, infection, and incisional hernia [4, 16]. The prolonged immunosuppression therapy can also result in diabetes, progressive renal insufficiency, hypertension, osteoporosis, post-transplant lymphoproliferative disorder, hypercholesterolemia, and malignancies [4, 17].

The increasing prevalence of hepatitis C, combined with steady improvements in survival rates following liver transplantation, has caused a marked increase in the demand for liver transplantation. The pool of eligible transplant recipients has also been expanded by advances in surgical techniques [11, 18]. Thus, the median waiting time for a liver transplant in the United States has increased from one month in 1998 to over one year in 2002, and patients now receive transplants much later in the course of their disease [16, 18]. However, the number of cadaveric organs donated has remained relatively stable for many years, and demand for cadaveric livers now far outstrips supply [19,20].

In an attempt to narrow this deficit, innovative surgical techniques such as split liver transplantation were developed [4, 21]. This technique exploits the liver's unique ability to regenerate rapidly and regulate its own growth and mass according to the optimum liver/body mass ratio required by the recipient [22]. The procedure typically involves splitting the liver, either in situ or ex situ, into one extended right lobe graft for an adult recipient and one left lateral segment graft for a child. Liver graft volume doubles in seven days and is almost completely regenerated by 60 days post-transplant [22, 23].

A modified split liver technique has been used to supply grafts for two adults, but achieving an adequately sized left lobe graft often compromises the function of the right lobe graft [3]. Consequently, split liver grafts have had little impact on expanding the cadaveric donor pool for adults [24]. In addition, technical, logistic, and public policy issues have stymied the widespread use of this technique in North America to the extent that it comprises less than 2% of all liver transplant procedures [4, 21, 23]. The one

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year survival rate for patients receiving an extended right lobe cadaveric graft is comparable to that of whole liver transplant recipients [23].

Living Donor Liver Transplants

Of the 528 Canadians waiting for a liver transplant in 2002, 15% died before a donor organ became available [25]. Many patients also die when their condition deteriorates to the point that they are no longer eligible for a transplant [26]. The chronic donor liver shortage in most Western countries led to the search for new solutions, such as live donor liver transplantation (LDLT). Adult to adult LDLT generally involves resection of either a full left (segments II to IV) or a full right (segments V to VIII) donor hepatic lobe [27, 28].

LDLT developed from split liver transplantation and was first successfully performed in 1989 [24, 26]. It originally involved transplanting the left hepatic liver lobe of an adult (approximately 20% of the total liver mass) into a child, but the technique was soon extended to include small adult recipients [14, 24, 26]. In LDLT, a balance must be struck between providing the recipient with sufficient functional liver cell mass to survive and ensuring an adequate residual liver volume in the donor. It is generally accepted that the donor hepatectomy should not exceed 70% of the total liver mass [29]. The graft should be at least 30% of the size of the recipient's normal liver volume or at least 0.8% of the recipient's body weight [10, 12, 29, 30]. However, these ratios are dependent on the recipient's condition, the quality of the graft, and the implantation technique [31]. Thus, the small size of left liver lobe grafts limits their use in LDLT to recipients that weigh less than 60 kilograms [28].

The first adult to adult LDLT of a right hepatic lobe, which constituted between 60% and 70% of the donor's total liver volume, was performed in Japan in 1994. The majority of LDLT procedures currently performed in North America involve right lobe grafts [9, 26]. The donor operation involves a cholecystectomy, after which the right hepatic lobe is removed, flushed with cold preserving solution, and prepared for transplantation. The divided vessels in the donor are then over sewn and the falciform ligament is reconstructed to avoid twisting of the remaining left liver lobe [18, 26, 28]. The recipient operation is similar to a cadaveric liver transplantation procedure except that the donor and recipient operations are usually performed in adjacent operating rooms to minimise the cold ischemic time of the liver graft [10, 18, 29, 31].

Adult to adult LDLT is now routinely offered in many Western countries [14]. The number of live transplants performed in the United States increased markedly from 56 procedures in 1996 to 509 in 2001, whereas the number of cadaveric transplants remained stable [9, 20, 26]. Similarly, 13% of all liver transplant operations performed in Canada in 2002 involved live donors [19].

Potential advantages and complications

The purported advantages of LDLT include a shorter waiting time for a liver transplant; the ability to schedule the operation electively and optimise the recipient's condition prior to transplantation; the option of performing a pre-transplantation cross match between donor and recipient; reduced cold ischemic time for the donor liver (from over 8 hours for a cadaveric liver to less than one hour for a live graft); and increased availability of cadaver livers for the patients still on the waiting list. Also, there is less likelihood of primary graft failure in the recipient since the graft is taken from a healthy, hemodynamically stable donor rather than from a donor who has just died from trauma or illness [10, 18, 26, 29, 31].

The range of complications experienced by LDLT recipients is similar to those associated with cadaveric graft procedures. However, LDLT has its own inherent problems. LDLT patients receive a smaller graft than cadaveric liver recipients and must rely on a smaller hepatic reserve until the graft has regenerated. In addition, the biliary and vascular anastomoses in LDLT are technically more difficult to perform than for whole organ transplantation, which increases the risk of biliary leaks, vascular thrombosis, and pulmonary embolism [18, 26].

Donation of a right lobe is associated with 0.5% to 1% mortality and 40% to 60% morbidity, whereas the risk of left lobe donation is far lower [14, 32]. In comparison, living kidney donors have a mortality risk of 0.03%, a 2% risk of major morbidity, and a 10% to 20% risk of minor morbidity [14]. Perioperative morbidity for live liver donors can include hepatic insufficiency or failure, portal vein thrombosis, deep vein thrombosis, bleeding, a need for blood transfusion, bile duct injury, bile leak, abscess, wound infection, incision pain, hernia, splenic injury, and late intestinal obstruction due to adhesions [9, 10, 18, 29, 31, 33].

Evidence for the Use of Adult to Adult LDLT

A summary of extracted data from selected studies is tabulated in Appendix A. The search strategy and study selection criteria are outlined in Appendices B and C.

Safety and Efficacy/Effectiveness

Recipient outcomes

To date, a systematic review of recipient outcomes following adult to adult LDLT has not been published. Numerous case series studies have been reported, but only three non-randomised comparative studies comparing LDLT with cadaveric transplantation were identified.

Gaglio et al. [34] assessed the outcomes of patients infected with hepatitis C virus (HCV) following either LDLT or whole liver cadaveric graft transplantation. There was no

discernible difference between the two patient groups with respect to the timing, incidence, or severity of HCV recurrence even though the LDLT patients were in better medical condition than those who received a cadaveric graft. More patients in the LDLT group developed cholestatic hepatitis C postoperatively, compared to those receiving a cadaveric graft. This suggests that the significant liver regeneration that occurs in LDLT recipients may promote HCV replication and recurrence, which is difficult to treat in transplant patients and may lower survival rates. Since liver biopsies were only performed in patients with abnormal serum transaminases, the study may have underestimated the rate of HCV recurrence in cadaveric graft recipients who had HCV and normal serum transaminases and overestimated it in LDLT patients with elevated transaminase levels due to liver regeneration. Also, the correlation between elevated serum transaminases and HCV recurrence is not definitive [34]. The negative effect of HCV recurrence on graft and patient survival may have also been ameliorated by the better overall condition of the LDLT patients, compared to the cadaveric graft recipients [34].

Another study by Park et al. [35] reported no difference between LDLT and cadaveric transplantation in terms of the number and type of biliary complications occurring in recipients, regardless of the type of biliary construction used in the transplant procedure.

Trotter et al. [36] reported that both LDLT and cadaveric graft recipients generally remained in hospital for nine to ten days. The patient survival and graft survival rates were similar between the two groups. The LDLT recipients waited a median of 140 days for a liver graft, compared to 406 days for cadaveric liver recipients.

Donor outcomes

One systematic review [37] summarised the evidence on donor outcomes published from January 1995 to June 2001. The 12 included studies comprised surgical case series and survey results from a number of countries. Donors remain in hospital for just over a week after LDLT and take an average of 13 weeks to completely recover. The overall mortality rate was 0.2%. Most centres reported morbidity in just under a quarter of donors, but rates of up to 67% were documented. The most common complications were bile leak, prolonged ileus, minor wound problems, and transient pressure sores. Other adverse effects included neuropraxia, pleural effusion, pulmonary edema, and atelectasis. The majority of complications were treated conservatively, but an occasional patient required reoperation. Two small studies assessed donor quality of life and found that nearly all donors reported a benefit from participating in LDLT and no diminution in physical and social activity, or emotional stability.

The search strategy of this review was not very comprehensive since only one medical literature database was scanned and non-English language articles were not included. The review noted a number of deficiencies in the evidence base. The lack of standard

definitions for postoperative morbidity has made it difficult to quantify. Some investigators include every minor complication while others only report what they deem to be a severe complication. There may also be a mismatch between donor and clinician perceptions of what constitutes a 'minor' complication, particularly in a patient who was otherwise healthy. In addition, the outcomes of donors who are excluded intraoperatively because of anatomical abnormalities, technical problems, or undetected pathology may be lost to data collection because no transplantation occurred. Similarly, data are also not collected on complications arising from the invasive procedures, such as liver biopsy and angiography, performed to evaluate donors. Only three of the studies included in the systematic review reported length of follow-up, which was generally short. Consequently, long-term donor outcomes are unknown [37].

Cost

One study [36] compared the cost of performing LDLT with that of cadaveric liver transplantation. Only cadaveric graft recipients and LDLT donor/recipient pairs with greater than one year follow-up after transplantation were included. Donor costs encompassed donor evaluation, right hepatectomy, and donor follow-up while recipient costs included medical care for 90 days prior to surgery, transplantation, and follow-up. Nearly three quarters of the donor cost was contributed by the hepatectomy. The cost of evaluating failed donors and successful donors comprised 6% and 13% of the total donor cost, respectively. The total comprehensive cost of LDLT was 21% higher than cadaveric transplantation, but this difference was not statistically significant. LDLT patients were selected based on the likelihood of their having a successful outcome, so the study was ostensibly biased in favour of LDLT [36].

Clinical Practice Guidelines and Position Statements

The American Society of Transplant Surgeons (ASTS) published a position paper on adult to adult LDLT in 2000 [29] that provides guidelines for donor and recipient selection, criteria for transplant centre planning, and suggested approaches for obtaining informed consent. The central tenet of the document is that the health and safety of the donor should be paramount when considering LDLT. Donors should be healthy, of legal age, have an emotional relationship with the recipient, be willing and able to comply with long-term follow-up, and have sufficient intellectual capacity to give informed consent. Evaluation of donors must be undertaken by a multidisciplinary team. This should incorporate an assessment to ensure that donors fully understand the procedure, and its associated risks, and are not coerced. The recipient should be medically suitable according to standard criteria and must understand the risk incurred by the donor. LDLT should not be performed when the recipient has a poor chance of survival. The ASTS recommended that centres performing LDLT have an appropriate informed consent process, a proven need for

establishing an LDLT program, prior experience in liver transplantation and hepatobiliary surgery, and ongoing oversight. It was suggested that the ASTS should implement a national registry of all LDLT procedures.

The Live Organ Donor Consensus Group was sponsored by the National Kidney Foundation and the American Societies of Transplantation, Transplant Surgeons, and Nephrology to evaluate the current practice of live donor organ transplantation. A national consensus conference was convened to establish practice guidelines that address the social, ethical, and medical aspects of donors participating in live donor organ transplantation. Although the final document [27] was more comprehensive than the position paper released by the ASTS [29], the recommendations were the same.

Expert Opinion

Expert opinion was obtained from a general surgeon in Ontario who has expertise in LDLT. Since there are many types of ESLD, there is no single standard treatment for this illness. In Canada, LDLT is an optional treatment for ESLD that is neither experimental nor standard of care. The indications for LDLT are the same as for cadaveric transplantation. However, LDLT is considered to be most appropriate for patients who are still eligible for a transplant but whose condition is likely to deteriorate rapidly without treatment. The surgical expert was not aware of any ongoing North American study on the use of LDLT. It is unclear whether transplant surgeons in Canada support the expansion of LDLT or would prefer to see efforts directed at increasing the cadaveric donor liver pool since no survey data are available on this issue.

Ongoing Research

In October 2002 the United States National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases, in partnership with the ASTS and the Health Resources and Services Administration, launched the Adult to Adult Living Donor Liver Transplant Cohort Study (A2ALL). The study, which will involve ten medical centres nationwide over the next seven years, will compare the outcomes of donor/recipient pairs undergoing LDLT with a cohort of cadaveric graft recipients [38, 39].

The Canadian Council for Donation and Transplantation is currently conducting a Live Organ Donation Survey to identify the policies, practices, experiences, and perceptions related to live organ donation in Canada. A range of stakeholder perspectives will be canvassed including those of government, non-profit organisations, donation programs, health professionals, and donors. The report is scheduled for release in June 2004.

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical is currently conducting a comprehensive systematic review of adult to adult LDLT that will encompass both donor and recipient outcomes. It is expected that this will be published towards the end of 2004 (personal communication P. Middleton). The

Canadian Coordinating Office of Health Technology Assessment conducted a pre-assessment of LDLT in October 2003 [40], but is not planning any further work on this topic in the near future (personal communication L. Topfer).

Discussion and Conclusions

Safety and Efficacy/Effectiveness of Adult to Adult LDLT

Two studies [35, 36] found no discernible difference between either LDLT or cadaveric transplant recipients in terms of mortality, the number and type of postoperative biliary complications, graft survival rates, or length of hospital stay. There was some suggestion that transplant recipients infected with HCV prior to surgery were more likely to develop cholestatic hepatitis C after LDLT than they were after cadaveric graft transplantation [34]. Although the length of follow-up ranged from 12 to 26 months, the limited focus of these three studies does not allow a comprehensive comparison of recipient outcomes following LDLT and cadaveric donation.

One systematic review [37] addressed donor outcomes but its results are outdated. Nonetheless, it provides a useful preliminary outline of the living liver donor experience. On average, donor convalescence takes just over three months. Up to 0.2% of donors die from the LDLT procedure, and at least a quarter of donors experience adverse effects ranging from bile leak and wound problems to more serious complications such as blood clots and small bowel obstruction. A small subset of donors reported prolonged minor symptoms but no other deleterious effects on their quality of life following LDLT.

The assessment of LDLT is problematic because of limitations inherent in the evidence base. The ethical imperative of wisely using a liver graft from a living donor means that LDLT is usually performed in recipients who are specifically chosen as having the best chance of a favourable outcome. Consequently, direct comparisons between these elective patients and the recipients of cadaveric transplants who undergo emergency transplantation and are generally sicker at the time of surgery can be misleading [26]. In addition, the variability in surgical technique, operative skill, and extent of liver resection among transplant centres also limits intra- and inter-study comparisons [37].

The true incidence of morbidity and mortality for right liver grafts is unknown because the majority of case series studies published to date include a large contingent of live donations performed between adults and children and adult to adult donation of left liver grafts [41]. In addition, there is some concern that the published literature is somewhat sanguine with respect to donor outcomes because it is largely based on centre surveys [37]. However, this potential underestimation of donor morbidity is counterbalanced by the fact that donors who are followed up frequently after donation are more likely to report complications because of their increased contact with clinicians [37].

Generally, donor evaluation is a step wise process that assesses donors for overall health, blood group compatibility, and any underlying medical condition that may preclude donation. The donor then undergoes psychosocial evaluation to confirm informed consent and ensure that the decision to donate is free of coercion. One survey of transplant centres in the United States reported that the median evaluation time for potential donors was 28 days (range 7 to 84), with the minimum time ranging from 1 to 56 days (median 6.5) [42]. Only 45% of potential donors eventually donated (range 8% to 100%). In the United States, 60% of transplant centres perform an arteriogram on all donors and just over a quarter conduct liver biopsies on donors as part of the routine medical evaluation [42]. However, donor morbidity resulting from the evaluation process is rarely reported.

There is significant variability between centres in their postoperative follow-up of donors. A survey of transplant centres in the United States found that just over two thirds had a formal donor follow-up protocol [43]. The comprehensiveness of these protocols was diverse and only 34% of programs systematically tracked donor complications over time. The evidence base also suffers from the absence of a clear definition of what constitutes an adverse effect after liver transplantation. Thus, the data currently available on donor outcomes is far from complete.

Cost

One study [36] found that there was no discernible difference between LDLT and cadaveric graft transplantation with respect to the total comprehensive cost incurred from 90 days prior to surgery to one year post-surgery at a tertiary medical centre, even though the proportion contributed by various aspects of the procedures to the overall cost was different [36]. However, there are many other cost considerations that are not captured in these analyses. A more comprehensive, system wide approach is need to assess the opportunity cost of the health resources that are diverted to care for the LDLT donor, especially since they are not required by the cadaveric organ donor. Also, in most countries direct financial compensation for organ donation is illegal, but it is important that living donors do not bear any of the costs associated with donation. Nonetheless, some donors may incur costs of up to US$3660 [37] Even if the recipient's medical insurer pays for all of the medical charges associated with donor evaluation and hepatectomy, it is not always clear what happens after surgery if the donor requires ongoing care for health problems related to donation. The potential long-term impact of LDLT on donors with respect to future illnesses, ability to obtain life insurance, lost earnings due to poor health, and future employment opportunities is also unknown [14, 33].

Controversial aspects

The main impetus for developing LDLT was to offset the shortage of cadaveric organs rather than to overcome shortcomings in the cadaveric transplant procedure [44, 45]. In

fact, transplanting a segmental graft from a living donor is more technically challenging than the implantation of a full sized liver from a cadaveric donor. Therefore, any advantage conferred by LDLT with respect to better organ quality and shorter ischemic time is potentially offset by the technical disadvantages. A Markov decision model analysis found that LDLT only offered an advantage over cadaveric transplantation when the waiting time for a cadaveric graft exceeded seven months and there was a high probability that wait listed patients would develop contraindications to transplantation [45].

The impact of LDLT on liver transplant waiting lists is unknown. However, it is unlikely that LDLT will solve the chronic shortage of liver grafts since as few as 13% of recipients find a suitable donor within the first year of listing, compared to 39% of patients waiting for a cadaveric liver [31, 46]. There is also doubt surrounding the ethics of unrelated live liver graft donation. Live organ donation was once restricted to donors with a genetic link to the recipient, but improvements in immunosuppression have extended this option to unrelated individuals who have an emotional relationship with the recipient [27]. More than a fifth of live grafts now come from so called Good Samaritan donations in which the donor is unrelated to the recipient [47]. There is concern that this trend will result in the potentially unethical practice of accepting live liver grafts from donors who have no emotional attachment to the recipient whatsoever.

Indications for accepting recipients for LDLT remain controversial. The determination of suitability for transplant is based on an assessment of the severity of liver failure, the prognosis of the patient with current medical/surgical therapy, the patient's current quality of life, and the potential of the transplant to restore the patient's health [11]. LDLT is particularly suited for patients who are still in generally good condition and have a reasonable chance of a favourable outcome but who are at high risk of rapid deterioration or a long wait for a cadaveric transplant [26, 31, 48]. In the United States and Europe there is general agreement that live donation should only be offered to patients who meet the criteria for cadaveric transplantation, particularly since LDLT recipients may need an urgent cadaveric liver transplant if the live graft fails [26,41]. Nevertheless, debate continues over whether LDLT should be offered to recipients who do not meet the accepted criteria for cadaveric organ donation [14, 49, 50].

The ethical issues surrounding LDLT include the need for: autonomy of the donor and the recipient; an environment where the donor is not subject to coercion; and informed donor consent supported by a true estimate of the utility of LDLT and donor complication rates, and the identification of any future physical and financial risks for the donor. The ethics of performing LDLT when the recipient has fulminant liver failure are also questionable because the urgent nature of the procedure often precludes adequate screening and education of the donor. Thus, it is almost impossible for the donor to make a properly informed decision that is free from coercion [9, 14]. Adequately

addressing these issues is difficult given the current lack of agreement on many aspects of the LDLT procedure. In addition, there are no standard protocols for the preoperative evaluation of potential donors, and postoperative donor follow-up is generally ad hoc and rarely includes psychosocial evaluation or support [37, 43]. This may need further examination since it has been noted that a donor whose recipient experiences major complications generally has a lower mental health scale score than a donor whose recipient fares well after LDLT [51].

There is a significant learning curve associated with performing LDLT and procedure volume is positively correlated with patient outcome [41]. It is generally agreed that LDLT should not be performed at centres conducting fewer than 20 liver transplants per year and that any surgical team undertaking LDLT should be experienced in hepatobiliary surgery, as well as whole and split cadaveric liver transplantation [9, 11, 31, 52]. However, a recent survey of liver transplantation centres in the United States found that over a third of active transplant programs had performed fewer than ten living donor right lobectomies [43]. This is of great concern, particularly in the United States where centres are under considerable competitive pressure to offer this procedure.

The future of adult to adult LDLT

On the basis of current selection criteria, only 5% of patients requiring a liver transplant will be both medically eligible to undergo LDLT and able to identify a suitable donor [26]. Given that 20% to 30% of people currently suffering from chronic HCV infection will require a liver transplant within the next ten years [30], LDLT is clearly not the solution to the cadaveric liver shortage. LDLT will remain an optional procedure that is available only to select patients with ESLD [26].

In Canada, 12.1 liver transplants were performed per million people in 2002, which is much lower than the US rate of 18.3 and is largely due to the lower cadaveric donation rates in Canada [19]. Thus, it is important to continue initiatives aimed at increasing consent rates for cadaveric organ donation in order to decrease the need for LDLT. Future developments in transplant surgery may expand the use of domino transplants and grafts from non-beating heart or marginal donors, such as those who are obese [13, 14, 53]. Innovative surgical techniques, including the application of split liver grafts to two adult recipients, the use of dual left grafts from two donors, and right posterior liver grafts (segments VI and VII) also hold promise [13, 14, 28, 53]. In the long-term, tissue engineering, hepatocyte and stem cell transplantation, gene therapy, bioartificial liver, extracorporeal liver support, and xenotransplantation may offer alternative treatments for liver failure that could obviate the need for LDLT [6, 9, 13, 23, 54].

Despite its popularity, the evidence base for LDLT is incomplete. LDLT is a relatively new procedure and is still undergoing active development, so its safety and efficacy relative to cadaveric liver transplantation and its impact on liver transplant waiting lists

are unknown. Many countries are scurrying to establish databases to fill the substantial knowledge gaps associated with this procedure, and research continues apace. Accreditation criteria outlining the minimum expertise required before a centre can offer LDLT are needed to ensure the safe diffusion of this technique. Future research on LDLT has a twofold imperative. Safety must be demonstrated, not only for the recipient of the live liver graft but also for the donor. Since the current evidence does not suggest that LDLT is superior to cadaveric transplantation, it is reasonable to assume that LDLT would not be performed if there was an abundant supply of cadaveric organs. Therefore, future initiatives in LDLT must aim to achieve minimal morbidity and zero mortality for donors, and ensure that the risk to the donor is never outweighed by the benefit to the recipient.

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APPENDIX A: SUMMARY OF RECIPIENT OUTCOMES – COMPARATIVE STUDIES

Authors/ Location	Intervention	Study Design	Study Population	Results	Comments
Gaglio et al. (2003) [34] United States	**1) Cadaveric liver transplantation** No details reported. **2) Live donor liver transplantation** No details reported. **1) & 2)** The postoperative immunosuppression protocol and treatment of acute cellular rejection was standardised for all patients.	Retrospective non-randomised study with concurrent controls **Median Follow-up:** **1)** 26 months; **2)** 24 months **Setting:** University affiliated liver transplant centre **Study Period:** December 1998 to March 2002 **Outcome Measures:** Incidence, timing, and severity of histologic recurrence of hepatitis C virus (HCV)	**Sample Size: 1)** n = 45; **2)** n = 23 **Patient Diagnosis:** HCV infected patients requiring a liver transplant for HCV associated cirrhosis. Four patients in group 1 and five in group 2 had hepatocellular carcinoma. **Mean Age:1)** 56 years; **2)** 57 years **Gender Mix:** **1)** M/F = 31 (68.9%)/14 (31.1%) **2)** M/F = 14 (60.9%)/9 (39.1%) **Repeat Resections:** Not stated **Inclusion Criteria:** HCV infected patients who required a liver transplant for HCV associated cirrhosis. **Exclusion Criteria:** Patients ≤ 18 years old	**Mortality: 1)** 8.9%; **2)** 13.0% **Patient Survival (1, 2, and 3 year): 1)** 94%, 89%, 85% **2)** 95%, 87%, 84% **Graft Survival (1, 2, and 3 year): 1)** 90%, 85%, 80% **2)** 92%, 87%, 83% **Acute Rejection:** **1)** 62% **2)** 61% (p not significant) **HCV Recurrence:** **1)** 69%; **2)** 79% (p = 0.3) **Mean Time to Recurrence:** **1)** 22 weeks **2)** 16 weeks (p = 0.3) **Developed Cholestatic Hepatitis C:** **1)** 0%; **2)** 17% (p = 0.001)	Retrospective study design. Patients receiving cadaveric transplants had a significantly higher MELD score than those undergoing live donor transplantation (p = 0.001). Postoperative liver biopsies not performed in all patients.
Park et al. (2003) [35] Korea	**1) Cadaveric liver transplantation** No details reported. **2) Live donor liver transplantation** No details reported. **1) & 2)** Biliary reconstruction was by choledochocholedochostomy and/or hepaticojejunostomy depending on various anatomical and patient factors.	Retrospective non-randomised study with concurrent controls **Median Follow-up:** **1) & 2)** 20 months (range 4 to 53) **Setting:** University affiliated medical centre **Study Period:** January 1992 to June 2001 **Outcome Measures:** Frequency and type of biliary complications	**Sample Size: 1)** n = 103; **2)** n = 326 **Patient Diagnosis:** Not stated **Age:1) & 2)** Range 18 to 65 years **Gender Mix:** Not stated **Repeat Resections:** Not stated **Inclusion Criteria:** All patients who underwent liver transplantation during the study period were included.	**Biliary Complication:** **1)** 5.8%; **2)** 5.8%* **Biliary Stricture:** **1)** 3.9% **2)** 4.9% (p not significant) **Biliary Stone:** **1)** 2.9% **2)** 2.2% (p not significant) **Bile Leak:** **1)** 1.9% **2)** 2.2% (p not significant)	Retrospective study design. Only reported biliary complications. Details of postoperative management were not provided. Baseline patient information was not reported. It is likely that confounding prognostic factors were unevenly distributed between the treatment groups. Results may be confounded by practice changes that are likely to have occurred over the long study period.

*One patient received a cadaveric and living donor graft.

MELD – Model for End Stage Liver Disease (lower scores indicate better overall medical condition)

Summary of Recipient Outcomes – Comparative Studies (cont'd)

Authors/ Location	Intervention	Study Design	Study Population	Results	Comments
Trotter et al. (2003) [36] United States	**1) Cadaveric liver transplantation** No details reported. **2) Live donor liver transplantation** Adult to adult right hepatic lobe graft.	Non-randomised comparative study with concurrent controls. Cadaveric graft recipients were randomly selected. **Follow-up:** **1) & 2)** 12 months **Setting:** University affiliated medical centre **Study Period:** **1)** August 1997 to June 2000; **2)** 1997 to 1999 **Outcome Measures:** Graft survival, patient survival, re-transplant rate, costs for all medical care	**Sample Size: 1)** n = 43; **2)** n = 24 **Patient Diagnosis:** **1)** Hepatitis C (37.2%), alcoholic cirrhosis (16.3%), primary biliary cirrhosis (7.0%), autoimmune hepatitis (2.2%), sclerosing cholangitis (14.0%), cryptogenic (14.0%), other (9.3%); **2)** Hepatitis C (50.0%), autoimmune hepatitis (8.3%), sclerosing cholangitis (16.7%), cryptogenic (8.3%), other (16.7%). **Mean Age:** **1)** 50.9 years (SD ± 9.6) **2)** 45.0 years (SD ± 9.5) **Gender Mix:** **1)** M/F = 30 (70%)/13 (30%) **2)** M/F = 11 (45.8%)/13 (54.2%) **Repeat Resections:** Not stated **Inclusion Criteria:** Patients receiving either a right hepatic lobe from a living donor or a cadaveric liver who had at least one year post-transplantation follow-up.	**Mean Length of Hospital Stay:** **1)** 12.5 days (SD ± 12.7); **2)** 18.1 days (SD ± 18.5) (p=0.15) **Median Length of Hospital Stay:** **1)** 9 days; **2)** 10 days (p>0.05) **Patient Survival:** **1)** 95.4%; **2)** 91.7% (p>0.05) **Graft Survival:** **1)** 86.1%; **2)** 83.3% (p>0.05) **Re-transplantation Rate:** **1)** 13.9%; **2)** 16.7% (p>0.05) The total comprehensive cost of living donor liver transplantation was 21% higher than cadaveric transplantation, which is roughly equivalent to an extra US$25,000 to US$30,000. This difference was not statistically significant.	Only living donor liver transplant recipient pairs with greater than one year follow-up after transplantation were included. Thus, only 24 pairs were included from a potential pool of 49. There were significantly more males in group 1 (p<0.05) than in group 2. Group 1 recipients were also older (p=0.02). Costs were reported as relative cost units because the publication of actual costs was prohibited by the authors' institution.

SD – standard deviation

SUMMARY OF DONOR OUTCOMES - SYSTEMATIC REVIEWS

Review Details	Intervention/ Comparison	Study Population	Key Results/Conclusions	Authors' Conclusions
Beavers et al. (2002) [37] **Studies Reviewed:** 12 independent case series and survey studies (6 from North America, 4 from Asia, and 2 from Europe). **Quality Scoring:** Not applicable. **Inclusion Criteria:** Studies published in English of liver donors undergoing right lobectomy for donation to recipients 18 years or older. **Exclusion Criteria:** Studies that reviewed other sources of primary patient data.	**Comparisons:** Not applicable **Outcomes Measured:** Included postoperative complications, length of hospital stay, readmission rate, recovery time, return to pre-donation occupation, health related quality of life, or mortality.	**Sample Size:** n = 409 donors **Patient Diagnosis:** Not applicable **Age:** Not reported **Gender Mix:** Not reported **Follow-up Range:** 8.3 to 13.7 months (3 studies)	**Donor outcomes:** Mean length of hospital stay (9.9 days, 8 studies); readmission rate (6.2%, n = 65); mortality (0% to 0.2%); mean time to complete recovery (13 weeks, range 4 to 52; n = 14); return to work (98.3%, n = 60). **Complications:** Most centres reported <24%, range 0% to 67%. The most common postoperative adverse events were bile leak, prolonged ileus, minor wound problems, and transient pressure sores. **Quality of Life (3 studies):** a) 24 donors: mild persistent symptoms (17%), primarily abdominal discomfort; reported a benefit from the donor experience (96%). b) 14 donors: no significant change in physical activity, social activity, or emotional stability.	Interpretation of results was limited by the lack of a standardised definition of morbidity. Future studies should systematically assess donor morbidity by using standardised definitions. Donor morbidity should be included in a national database. Donor morbidity reports should include all liver donors. Minimum length of follow-up should be six months. Measurements should also include economic and health related quality of life outcomes in addition to medical complications.

APPENDIX B: SEARCH STRATEGY

Table B.1 lists the databases and information sources searched to identify literature and related materials. The bibliographies of all publications retrieved in full hard copy form were manually searched for relevant references that may have been missed in the database searches.

Table B.1: Search strategy for studies on LDLT

Database	Platform	Edition	Search Terms†
Cochrane Library		Issue 4, 2003	(living OR live OR living donor*) AND (liver transplantation OR liver transplant*)
CINAHL	Ovid	January Week 1/1982 to December Week 2/2003	(Exp transplant donors/ OR living donors.mp OR live donor$.mp) AND (liver transplantation.mp OR exp liver transplantation/)
EBM Reviews – ACP Journal Club	Ovid	January 1991 to July/August 2003	living donor.mp OR living donors.mp OR live donor*.mp
EMBASE	Ovid	Week 1/1988 to Week 50/2003	((living donor.mp OR exp living donor/) AND liver transplantation.mp OR exp liver transplantation/) NOT case report.mp
HealthSTAR	Ovid	January 1987 to November 2003	(living donors.mp OR exp living donors/ OR live donor.mp OR LDLT.mp OR LURD.mp) AND (liver transplantation.mp OR exp liver transplantation/)
PubMed	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=icauahslib	December 18, 2003	((living donors OR "live donor*" OR "living donor*" OR LDLT OR LURD) AND (liver transplantation OR "liver transplant*") AND (clinical trial OR editorial OR meta-analysis OR practice guideline OR randomized controlled trial OR review OR systematic [sb] OR in process [sb])) NOT case reports [pt]
Science Citation Index	Web of Science	December 19, 2003	(living donor* OR live donor) AND liver transplant*
NHS CRD (UK)	http://nhscrd.york.ac.uk	December 19, 2003	liver AND (living-donors OR living donor*)
HTA agencies, research registers, and guidelines sites		January 2004	Searched as per the CCOHTA HTA Checklist.
Additional Internet sites checked and search engines used		January 2004	ECRI and the NEOS library consortium. www.google.com www.copernic.com

Note: * is a truncation character that retrieves all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc. In databases accessed via the Ovid platform the truncation character is $; †Searches limited to human and English language studies published from 1995 onwards.

APPENDIX C: METHODOLOGY

Inclusion and Exclusion Criteria

Types of Studies

Only systematic reviews or comparative studies, with at least ten patients in each study arm, published in English from 1995 onwards were included for analysis. An article was deemed to be a systematic review if it met all of the following criteria as defined by Cook et al. [55]:

1) focused clinical question;
2) explicit search strategy;
3) use of explicit, reproducible, and uniformly applied criteria for article selection;
4) critical appraisal of the included studies;
5) qualitative or quantitative data synthesis.

Participants

Data were collected on adult (≥ 18 years of age) patients receiving a liver transplant from an adult live donor for any indication. Patients receiving any other organ transplant in addition to the liver graft were excluded. Animal studies were not included.

Index Intervention

Any form of liver transplant where the graft is harvested from a living donor.

Comparator intervention

Any form of liver transplant where the graft is harvested from a cadaveric donor.

Outcomes

The included studies must contain information on at least one of the following outcomes for both the index and comparator intervention: perioperative and postoperative mortality or morbidity, graft survival rate, convalescence interval, quality of life, or liver function.

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